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(54) Title: TRANSDERMAL APPLICATION AGENT CONTAINING ESTERS OF 3-KETODESOGESTREL

(57) Abstract

An agent for transdermal application characterized in that it contains esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with 1 to 20,carbon atoms in the ester group, optionally in combination with 1 or 2 estrogens.

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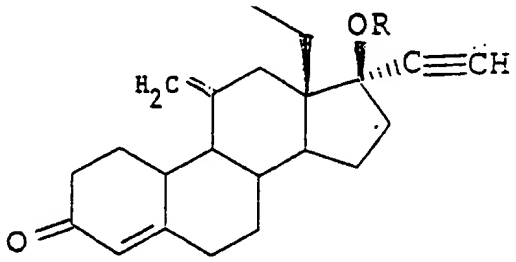
AGENT FOR TRANSDERMAL APPLICATION CONTAINING ESTERS OF 3-KETODESOGESTREL

The invention concerns an agent for transdermal applications, which is characterized in that it contains esters of
13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 1 to 20 carbon atoms in the ester group, optionally in combination with one or more estrogen(s).

These esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one are characterized by the generic formula



in which R is an acyl group with 1 to 20 carbon atoms.

In particular, the invention concerns such transdermal application agents containing esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 2 to 12 carbon atoms in the acyl group and especially agents containing alkanoyl esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 2 to 8 carbon atoms in the alkanoyl group. As, heretofore unknown, suitable esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one being stressed in particular are their acetates, their butyrates and preferably their hexanoates, which are likewise the subject of the present invention and the production of which is described later.

13-Ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one itself is a known substance with extraordinarily high gestagenic activity which in the form of its Pro-drug 13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene--17?-ol (J. Of Steroid Biochem., 14, 1981, 175 pp and Europ. J. Clin. Pharmakol., 15, 1979, 449 pp) in combination with estrogen effective

compounds are used for producing oral application agents with conception prevention action (Marvelon®).

It is now found surprisingly that the esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, optionally in combination with 1 or more estrogens can be used for producing a transdermal application agent of active material, in some cases often better, than combination preparations, which themselves contain esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one.

By esterification of the 17β-position hydroxyl group of the esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one the physical chemical properties of this substance are directed and bio-reversibly changed in the direction of a Pro-drug- structure.

Upon comparing the skin penetration of the esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with that of their esters, thus the latter distinguishing itself in general by the clearly higher transdermal flow. Above all, this is valuable in the performance of the ester in Matrix-Transdermal systems, like, by way of example, Acrylate Type (as they are described later in Example 2).

The astonishingly high transdermal flow is clearly preferable to the surprisingly convenient solubility, which, for the named esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, is present in the ordinary skin contact adhesive and their mixtures with co-solvents or penetration enhancers. On the basis of this property now highly charged and stable matrix transdermal systems can be produced with molecular dispersion distributing Pro-drugs. Self-active material charges, which on a molecular basis are around the factor 15 higher than that comparable, even realizable, for 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, lead to stable systems. This is a distinct advantage over 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one containing systems which are previously known from WO94/04157, since the concentration level between transdermal systems and the skin conclusively is responsible for the attainable height of the transdermal flow.

Thus, it is possible with help of agents according to the invention to obtain high uniform flows of esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with comparatively small transdermal systems.

It is already mentioned that the agent according to the invention, besides gestagens, can still contain 1 or more estrogens.. By way of example, suitable estrogens are estradiol, estriol, ethinylestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-tiene-3,17β-diol (WO 88/01275), 14 α,17α-ethanoestra-1,3,5(10)-tiene-3,16α17β-triol (WO 91/08219) and their esters (EP-A 163596), like estradioldipropionate, estradioldihexanoate and estradioldidecanoate. These preparation combinations contain beside 1 or 2 gestodenestern preferably 1 to 3 , especially 1 to 2 estrogens.

The active material or active material mixture can be dissolved or suspended in suitable volatile solvents and/or penetration-enhancing agents for producing pharmaceutical preparations,. The solvents or suspensions obtained can be mixed with the customary additives, like matrix builders and bactericides and, if necessary, after sterilization are emptied into dosing containers. On the other hand, it is also possible to process these solutions or suspensions further to lotions and salves by introducing emulsifiers and water. One can also – optionally with the addition of fuel gas – produce Sprays that can be filled in customary dosing containers.

Suitable volatile solutions, by way of example, are low molecular weight alcohols, ketones or low molecular weight carboxylic acid esters like ethanol, isopropanol, acetone or ethylacetate, polar ether, like tetrahydrofuran, low molecular weight hydrocarbons, like n-hexane, cyclohexane or benzene or halogen hydrocarbon as well, like dichloromethane, trichloromethane, trichlorotrifluoroethane and trichrolofluoromethane. It is not necessary to explain that mixtures of these solvents are also suitable.

Suitable penetration-enhancing agents are, by way of example, 1 or more valent alcohol(s), like ethanol, 1,2-propandiol or benzyl alcohol , saturated and unsaturated fatty alcohols with 8 to 18 carbon atoms, like lauryl alcohol or cetyl alcohol, hydrocarbons, like mineral oils, saturated and unsaturated fatty acids with 8 to 18 carbon atoms, like stearic acid or oleic acid, fatty acid esters with up to 24 carbon atoms or dicarbolic acid diesters with up to 24 carbon atoms

Fatty acid esters, which are suitable penetration-enhancing agents, by way of example, are such as acetic acid, caproic acid, lauric acid, myristic acid, stearic acid, palmitic acid or oleic acid , like for example the methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, secondary-butyl esters, isobutyl esters, tertiary-butyl esters or monoglyceroesters of these acids. Especially preferred esters are those of mystiric acid or oleic acid, like their methyl esters, isopropyl esters or monogylceroesters. Suitable dicarboxylic acid esters are, by way of example, diisopropyladipate, diisobutyladipate and diisopropylsebacate.

Additional penetration-enhancing agents are phosphate derivatives, like lecitin, terpenes, amides, ketones, ureas and their derivatives or ethers like, for example, diethylene glycol monoethyl ether or dimethyl isosorbit. There is no need to explain further that mixtures of these penetration-enhancing agents are also suitable for producing agents according to the invention.

The concentration for the esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one in which the active materials or active material mixtures are optimally suspended or dissolved in the solvent agent, is usually 0.01 to 50 % by wt. In the estrogens the concentration is normally dependent upon the type active material used and the individual doses sought, in each case it must be done by means of preliminary experiments by the specialist, like, for example, the determination of the attainable active material concentration in the plasma, after selected dermal applications of the system, according to the invention, are found. Here, in general, the active material concentrations from 0.01 to 25 % by wt. of estrogen in the agent, according to the invention, are also satisfactory. The weight relationship of the esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one to the 1 or more estrogen(s) in the preparation combination is 5:1 to 1:10.

The daily dose therapeutic requirement of transdermal is indication-dependent and is in the range of about 30-120?g of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one per day. The esters of 13-ethyl-17?-hexanoyloxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one are equi-molar doses, in order to allow for the increase in molecular weight by the Pro-drug-Structure. For example, the daily dose for the 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one is about 40-150?g. Reference to a

transdermal system with a $20cm^2$ surface means that transdermal flows of up to 0.3?g of the 13-ethyl-17?-hexanolyoxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one/cm^2/h are necessary. In in-vitro studies with known formulations it has been demonstrated that these were clearly dropping excessively.

A very similar application with adjusted dosages of active materials or active material mixtures can be obtained if the active material or the mixture is embedded in a transdermal therapeutic system (TTS). Suitable transdermal therapeutic systems are those which one normally uses for percutaneous applications of active materials (Yie W. Chien: "Transdermal Controlled Systemic Medications", Marcel Dekker, Inc., New York and Basel 1987, Dr. Richard Baker: "Analysis of Transdermal Drug Delivery Patents 1934 to 1984" and "Analysis of Recent Transdermal Delivery Patents, 1984-1986 and Enhancers Membrane Technology & Research 1030 Hamilton Court, Menlo Park, CA 94025 (415) 328-2228).

So, by way of example, one such transdermal therapeutic system can be used which consists of

a) an impermeable covering layer,
1 to 3 pasted to the covering layer, of 1 or more ester(s) of 13-ethyl
-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one

containing optionally 1 or more estrogen(s) and desirable penetration-enhancing agents, contact skin adhesive containing permeable self-adhesive or of a desirable penetration-enhancing agent coating for these components or surrounding Matrix layer(s), a removable protective layer, or

b) a covering provided with a contact adhesive containing desirable penetration-enhancing agents,
1 to 3 (at times) leaving uncovered contact adhesive edges, fastened to the contact adhesive by means of a cover, of 1 or more ester(s) of
13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one
matrix layer(s) containing optionally 1 or more estrogens and penetration-enhancing agents and a removable protective layer, or

c) an impermeable cover layer,
1 to 3 present on or in the protective layer, of 1 or more esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, medicine reservoir(s) containing optionally one or more estrogens and desirable penetration-enhancing agents,
1 to 3 skin contact adhesive layer containing permeable polymer layer(s) of a permeable optional penetration-enhancing agent for these components and a removable protective layer.

A transdermal therapeutic system according to variant a) describes a simple matrix system. It can be, by way of example, in a circular, oval or rectangular shape and be prepared as follows.

A solution or suspension of up to 40% by wt. of active material or active material mixture, 0-40% by wt. of a penetration enhancing agent, 30-70% by wt. of a customary medical adhesive filled with a suitably volatile solution to 100% by wt. is stretched into a flat impermeable adhesive layer. After drying, a second and even later possibly a third optional active material, penetration enhancing agent and adhesive containing layer can be attached to this layer and dried. Then the matrix system is provided with a removal protective layer.

One uses a customary medicine matrix constituent which after drying of the system does not or does not sufficiently adhere to the skin, so one can cover or enclose the system by raising the removable protection layer even more with a skin contact adhesive.

Suitable solvents and penetration enhancing agents, by way of example, possess the already mentioned fluidity of this type. Suitable as customary medicinal adhesives are, by way of example, polyacrylates, silicons, polyurethanes, blockpolymers, styrol-butadiene-copolymers as well as natural or synthetic rubbers, such as for example polyisobutylenes. Cellulose ethers, polyvinyl compounds or silicates are under consideration as additional matrix structures. For increasing the adhesiveness of the receiving matrix the customary additives could be added such as, for example, glutinous producing rosins and oils. Above and beyond that crystallization inhibitors could be added such as, for example Kollidon® VA 64 for increasing the

physical stability of the systems as described, by way of example, in WO 93/08797.

All foils are suitable as protection layers which are ordinarily used in therapeutic systems. Such foils, by way of example, are siliconized or fluoropolymer layers.

By way of example, one can use 10 to 100 µm thick polyethylene or polyether foils, selectively pigmented or metallized as cover layers in this system. The medicine layer raised hereupon is preferably a thickness of 2 to 500 µm. The delivery of the active material is preferably over a surface of 5 to 100cm ^{2}.

In multi-layered matrix systems, by way of example, in which the matrix can be applied to the impermeable adhesive layers in which are introduced 1 or more esters of 13-eth yl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one and optionally the penetration enhancers while the layer or layers under it contain the estrogens and optionally even penetration enhancers. Besides it is however also possible in such a transdermal system to arrange several active material-containing matrices side by side.

A transdermal therapeutic matrix system according to variant b can, by way of example, also be circular, oval or rectangular and be prepared as follows.

A covering is coated with a skin contact adhesive. Then 1 to 3 working areas with an impermeable covering is/are pasted to this pro TTS to provide 1 or more ester(s) of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, optionally 1 or more estrogens and penetration enhancing agents containing matrix layers so that the covering of a sufficient edge for attaching to the skin and in multiple areas sufficiently between spaces and it is provided with a removable protective layer. The materials used in these matrix systems can be the same as those mentioned in Variant a.

A transdermal therapeutic reservoir system according to Variant c, by way of example, can likewise be circular, oval or rectangular and are described as follows:

An impermeable foil is shaped by heat and/or tension so that one to three 0.1 to 3 ml bulging shape is formed. This is filled with an active material containing solvent or suspension having 1 - 50% by wt. of active material or active material mixture with a penetration-enhancing agent. The active material containing solution or suspension can also be thickened with up to 10% by wt. of matrix builders.

A fused or pasted permeable polymer layer serves as the covering of the reservoir for the skin, upon which a permeable skin contact adhesive layer and a removable protection layer are stuck.

The above-mentioned penetration-enhancing agents could be used in these systems. By way of example, a 20 to 200 ?m thick foil of cellulose esters, cellulose ethers, silicones or polyolefin compounds are used as permeable polymer layer. Through the variation in these polymer layers the diffusion velocity of the active materials or active material mixtures vary within a wider range.

The same materials are suitable as adhesives and protection layers which are described in the transdermal therapeutic systems according to variant **a**.

In the preparation of transdermal therapeutic systems with 2 or 3 arranged side-by-side active material containing matrix layers or medicine reservoirs it is often suitable to introduce in one, 1 or more esters of
13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one and in the other, 1 or more estrogen(s). In the cases of this type the active material-containing matrix systems or medicine reservoir containing not only different active materials but as well even additional, different penetration enhancing agents.

In the case of the matrix systems according to variant a or b one must take care to have a sufficient difference in the care area in order to stop any diffusion of active material at times into the other area. In the case of the reservoir systems according to variant c it is possible for individual reservoirs to be provided with different permeable polymer layers so the diffusion flow of the individual active materials at times meets the requirements.

Additional characteristics of the transdermal system according to the invention are explained on the basis of the annexed , but not in correct scale drawings.

Fig. 1 shows a cross-section through a circular matrix system surface according to variant **a** without the removable protective layer. It is composed of the impermeable cover layer **1** and the medicine containing matrix layer **2**.

Fig. 2 shows a cross-section through a matrix system surface according to variant **b** without the removable protective layer. Fig. 3 shows the top view to these systems. The system consists of the covering **3** that is provided with a contact adhesive layer **4**. Two medicine containing matrix layers **6** and **8** are affixed to these contact adhesive layers by means of the impermeable coverings **5** and **7**.

Fig. 4 shows a cross-section through a round, single-chamber reservoir system according to **c** without the removable protective layer. It is composed of the impermeable layer **9**, the medicine reservoir **10**, the permeable polymer layer **11** and the skin contact adhesive layer **17**.

In addition, transdermal therapeutic systems are also suitable for further galenical preparations for transdermal application of the esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one.

An emulsion gel for transdermal applications consists of, by way of explanation, the active material or active material mixture, penetration enhancing agents, emulsifiers (in which ambiphile substituents of the penetration enhancing agents can serve as emulsifiers) and in such a case matrix formers. A typical receptor consists of 0.1 - 25% by wt. of active material or active material mixture, 0 - 10% by wt. of emulsifier, 0 - 5% by wt. of matrix former, 0 to 50% by wt. penetration enhancing agents and water to 100% by wt. The agent is emulsified in the usually manner and if necessary treated with the usual antioxidants, preservatives, etc.

Single-phase gels are obtained, by way of example, by dissolving or suspending the active material or active material mixture in solvents such as water, and secondary alcohols or mixtures of them, if necessary, addition of penetration-enhancing agents and thickening with matrix formers.

Typical receptors for such gels containing 0.01 - 25% by wt. of active material or active material mixture, 0 to 40% by wt. of penetration enhancing agent supplied with up to 100% solvent.

Also, the gels can contain, as desired, antioxidants, preservatives, etc.

A typical spray receptor, by way of example, is:

1 - 25% by wt. of active material or active material mixture, 0 - 20% by wt. of matrix former, 0 - 60% of penetration enhancing agent supplied with solvents and if necessary purgatives up to 100%. Pressure gas packs are used so the purgatives can escape.

The esters, according to the invention, of 13-ethyl-17ß-hydroxy-11-methylene-18, 19-dinor-17?-pregn-4-ene-20-yne-3-one containing agents for transdermal application can be used for treating similar illnesses, such as the previously known, by way of example, orally administering agent containing highly active gestagens. Beyond that, if necessary, the estrogen containing preparation can be found as well being used for contraceptives. The agents, according to the invention, are especially advantageous in the treatment of illnesses that require a long-term treatment with relatively high doses of the active material. Here, the application frequency can be substantially reduced and a corresponding blood plasma tolerance gel be substantially increased. A further advantage is that the gastrointestinal secondary effects are not to be expected and the first liver passage is by-passed in estrogen containing preparation combinations and that the doses can be reduced by estrogen.

These advantages allow the estrogen-free monotherapeutics of the previous invention to appear as especially suitable to, by way of example, treat endometriosis, gestagen dependent tumors, benign breast illnesses or premenstrual syndrome.

The transdermal use of estrogen in sequential or continuous combination with esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one are especially advantageous, by way of example, for treating climatic maladies, for preparation of osteoporoses, cycle regulation and cycle stabilization.

The following explanatory examples serve to more clearly explain the invention. The following commercial products are used in them:

0.074 mm thick polyester foil (Skotchpak® manufactured by 3M; polypropylene foil (Celgard® 2500) manufactured by Celanese, Liner foil Skotchpak® 1022 and 1360 manufactured by 3M; Transfer Adhesive 9871 manufactured by 3M, Sichello® type J 6610-21 polyacrylic ester - adhesive manufactured by Henkel KG, Oppanol® type B15SF poly-isobutylene - adhesive manufactured by BASF, Monsanto Gelva® polyacrylate ester – adhesive, X-7-4502 type silicon adhesive material manufactured by Dow Corning and HXF Klucel® type hydroxypropyl cellulose manufactured by Hercules and Kollidon® 12PF as well as Kollidon® VA64 crystallization inhibitors manufactured by BASF.

A: Agent for transdermal application

Example 1

While stirring, one after the other 0.8 g of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one and 8.0 g of dimethyl isosorbit are introduced into 62.4 g of a 50% solution of silicon adhesive material in benzene. After degassing the preparation, the mixture is laid out on a polyester film by means of a coating device in such a way that after the removal of the volatile solvents a similar film of 40 g/m^2 of solid coating forms. Connection is covered with a fluoropolymeric layer polyester liner. The thus contained laminate is divided into 10 cm^2 area individual circular plasters by means of a stamping device and packed in aluminum foil. Fig. 1 shows a cross-section through this plaster without the polyester-liner. The plaster adheres to the skin after removal of the liner foil.

The content determination is a similar active material proportion in the agent of 0.08 mg/m^2.

Example 2

While stirring, 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one are introduced into 80 g of a 50% solution of polyacrylic acid ester in ethyl acetate (g:g) and prepared as described in Example 1.

The content determination is a similar active material proportion in the agent of 8 mg/m^2.

Example 3

While stirring, 5.0 g of 13-ethyl-17ß-hydroxy-11-methylene-18, 19 -dinor-17?-pregn-4-ene-20yne-3-one and 10.0 g isopropylmyristate are dissolved in 170 g of a 50% solution of polyisobutylene adhesive substance in acetone/benzene. After degassing the preparation, the solvent is drawn onto the polyester film by means of a coating device in such a way that after

the removal of the volatile solvent, a similar film of 100 g/m^{2}of solid coating formed. Connection is covered with a fluoropolymeric layer polyester liner. The thus contained laminate is divided into 10 cm^2 area individual plasters by means of a stamping device and packed in aluminum foil. After the removal of the liner foil the plaster adheres to the skin.

The content of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one in the agent is 0.5 mg/cm^2.

Example 4

While stirring, one after the other, 3. 5 g of estradiol, 3.5 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18, 19-dinor-17?-pregn-4-ene-20yne-3-one and 7.0 g isopropylmyristate are dissolved or suspended in 112 g of a 50% solution of polyacrylester adhesive substance in acetone/benzene. After degassing the preparation, the mixture is drawn out onto the polyester film by means of a coating device in such a way that after the removal of the volatile solvent, a similar film of 70 g/m^{2}of solid coating formed. Connection is covered with a siliconizing active material-free liner film. The thus contained laminate is divided into 5 cm^2 area individual plasters by means of a stamping device and packed in aluminum foil. After the removal of the liner foil the plaster adheres to the skin.

The content of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one in the agent is 0.5 mg/cm^2.

Example 5

Analogous to Example 1 are two different segment-like Matrix systems prepared that have the profiles illustrated in Fig. 2 and Fig. 3. The matrix I consists of the matrix **8** provided with a polyester foil **7** of the following composition 1.0 mg of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one, 5.0 mg isopropylmyristate, 34 mg of acrylate contact adhesive material and 10 mg of Kollidon® VA64 and had a surface area of 5 cm^2.

The matrix II consists of the matrix **6** provided with a polyester foil **5** of the following composition 2.0 mg of estradiol, 10.0 mg isopropylmyristate, 68 mg of acrylate contact adhesive material and 20 mg of Kollidon® VA64 and has a surface area of 10 cm^2.

Example 6

A 7.4 cm diameter polyester foil is shaped by means of tension and heat such that a circular bulge with a surface area of 10 cm^2 is formed. This is filled with 1 ml of a solution of 2.5 mg 17ß-butyryloxy- 13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one in dimethylisosorbit. A polypropylene or cellulose acetate butyrate foil is fused to the edge. According to the pressure per unit of time the sealing temperature is between 70°C and 100°C. The contact adhesive foil is transferred onto the permeable polymer layer. The plaster is provided with a liner and packed in aluminum foil.

Fig. 4 shows a cross-section through a plaster of this type without a liner.

Example 7

Analogous to Example 6 a polyester foil is shaped so that two half-circle shapes by means of a gate from one to the other, forms separate bulges with surface areas of 7.5 cm^2 each.

Reservoir I is filled with 0.75 ml of a suspension with 1.5 mg of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one in 1,2-propandiol and Reservoir II with 0.75 ml of one such with 3.5 mg of estradiol in 1, 2-propandiol. The additional finishing of the plasters follows as described in Example 5.

Figure 5 shows a cross-section through a plaster of the type without liner.

Example 8

0.2 g of estradiol, 0.02 g 17ß-butyryloxy- 13-ethyl-11-methylene-18,19-dinor -17?-pregn-4-ene-20yne-3-one, 10.0 g of 1,2-propandiol and 10.0 g isopropylmyristate, one after the other is dissolved in 76.78 g of ethanol (96% by vol.) or isopropanol. Then 3 g of hydroxypropyl cellulose solvent is added and the air degassed from it. After 2 hours the gel is emptied into aluminum tubes with triple inner protection lacquering.

The analysis reveals a homogeneous active material portion in the gel with values of 95% to 105% of the theoretical values.

Examples 9

20.00 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one are dissolved in 1000 g of isopropylmyristate, sterilized by filtration and emptied under aseptic conditions into a 5 ml medicine bottle.

B: Syntheses

Example 1

5 g of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one are suspended in 34.5 ml (150 mmol) hexanoic acid anhydride, mixed with 1.04 g N,N-dimethylaminopyridine and stirred for an hour at 0°C and another 8 hours at 20°C. Then the mixture is chilled again at 0°C, mixed with 2.0 g calcium carbonate and 12.5 ml of methanol, stirred for 3 hours and mixed with 10 ml of water. The mixture is extracted with ethyl acetate, then acetate-extract washed, then dried over sodium sulfate and degassed under vacuum. The residue is examined chromatographically over a silica gel prism with 100:0 to 80:20 hexane-ethyl acetate and 5.85 g of 13-ethyl-17ß-hexanoylo xy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one obtained with a melting point of 123-124°C .

Example 2

Under the conditions of Example 1, but using acetic anhydride, 17ß-acetyl-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with a melting point of 170-171°C is produced.

Example 3

Under the conditions of Example 1, but using butyric acid anhydride, 17ß-butyryloxy-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with a melting point of 118-119°C is produced.

Patent Claims

1. Agent for transdermal application, characterized in that it contains one to three esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with 1 to 20 carbon atoms in the ester group optionally in combination with 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one and/or with 1 to 3 estrogens.

2. Agent for transdermal application according to Patent Claim 1, characterized in that it contains an ester of 13-ethyl-17ß-hydroxy-11-methylene-18, 19-dinor-17?-pregn-4-ene-20yne-3-one with 2 to 12 carbon atoms in the ester group.

3. Agent for transdermal application according to Patent Claims 1 and 2, characterized in that it contains 1 ester of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with 2 to 8 carbon atoms in the alkanoyl group.

4. Agent for transdermal application according to Patent Claims 1 to 3, characterized in that estradiol, estriol, 17?-ethinylestradiol, mestranol, 14?,17?-ethanoestra-1,3,5(10)-triene-3, 17?-diol, 14?,17?-ethanoestra-1,3,5(10)-triene-3,16?, 17ß-triol, mestranol or combinations of these esters are used as estrogen(s).

5. Agent for transdermal application according to Patent Claims 1 to 4, characterized in that the agent is a transdermal therapeutic system (TTS).

6. Agent for transdermal application according to Patent Claim 5, characterized in that the transdermal therapeutic system is composed of:

a) an impermeable covering layer,
1 to 3 pasted onto the covering layer, of 1 or more ester(s) of 13-ethyl -17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one containing optionally 1 or more estrogen(s) and desirable penetration-enhancing agents, contact skin adhesive containing permeable self-adhesive or of a desirable penetration-enhancing age nt coating for these

components or surrounding Matrix layer(s), a removable protective layer, or

b) a covering provided with a contact adhesive containing desirable penetration-enhancing agents,
1 to 3 (at times) leaving uncovered contact adhesive edges, fastened to the contact adhesive by means of a cover, of 1 or more ester(s) of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one matrix layer(s) containing optionally 1 or more estrogens and penetration-enhancing agents and a removable protective layer, or

c) an impermeable cover layer,
1 to 3 present on or in the protective layer, of 1 or more esters of 13-ethyl-17?-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one, medicine reservoir(s) containing optionally one or more estrogens and desirable penetration-enhancing agents,
1 to 3 skin contact adhesive layer containing permeable polymer layer(s) of a permeable optional penetration-enhancing agent for these components and a removable protective layer.

7. Agent for transdermal application according to Patent Claim 6, characterized in that it contains an active material ladened matrix layer or a medicine reservoir.

8. Agent for transdermal application according to Patent Claim 6, characterized in that it contains 2 or 3 active material ladened matrix layers or a medicine reservoir.

9. Agent for transdermal application according to Patent Claim 8, characterized in that it contains active material ladened matrix layers or the medicine reservoir of different active materials.

10. Use of esters of 13-ethyl-17ß-hydroxy-11-methyle ne-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 1 to 20 carbon atoms in the ester group optionally in combination with one or more estrogen(s) for producing the transdermal agent with active material or mixture of active materials.

11. Use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 1 to 20 carbon atoms in the ester group in combination with one or more estrogen(s) for producing an agent according to Patent Claim 10, characterized in that estradiol, estriol, 17?-ethinylestradiol, mestranol, 14?,17?-ethanoestra-1,3,5(10)-triene-3?, 17?-diol, 14?,17?-ethanoestra-1,3,5(10)-triene-3?,16?,17?-triol, or combinations of these esters are used as estrogen(s).

12. Use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 1 to 20 carbon atoms in the ester group in combination with one or more estrogen(s) for producing an agent according to Patent Claim 11 and 12, characterized in that the agent is a transdermal therapeutic system (TTS).

13. Use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20-yne-3-one with 1 to 20 carbon atoms in the ester group in combination with one or more estrogen(s) for producing an agent according to Patent Claim 12, characterized in that it is a transdermal therapeutic system according to Patent Claims 6 to 9.

14. Use of estrogen-free agents for transdermal applications according to Patent Claims 1 to 9 for transdermal contraception, treating of endometriosis, treating of gestagenic abhangiger tumors and treating premenstrual syndromes.

15. Use of transdermal application agents according to Patent Claims 1 to 9 optionally in combination estrogen -containing agents for treatment of climactic conditions, for prevention of osteoporosis, cyclic regulation, for cyclic stabilization and transdermal contraception.

16. Ester of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one with 2 to 8 carbon atoms in the alkanoyl group.

17. 17?-Acetoxy-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one

18. 17?-Butyryoxy-13-ethyl-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one

19. 13-Ethyl-17?-hexanoyloxy-11-methylene-18,19-dinor-17?-pregn-4-ene-20yne-3-one